# Consensus and variations in opinions on delirium care

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# Consensus and variations in opinions on delirium care: a survey of European delirium specialists

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ABSTRACT

**Background:** There are still substantial uncertainties over best practice in delirium care. The European Delirium Association (EDA) conducted a survey of its members and other interested parties on various aspects of delirium care.

**Methods:** The invitation to participate in the online survey was distributed among the EDA membership. The survey covered assessment, treatment of hyperactive and hypoactive delirium, and organizational management.

**Results:** A total of 200 responses were collected (United Kingdom 28.6%, Netherlands 25.3%, Italy 15%, Switzerland 9.7%, Germany 7.1%, Spain 3.8%, Portugal 2.5%, Ireland 2.5%, Sweden 0.6%, Denmark 0.6%, Austria 0.6%, and others 3.2%). Most of the responders were doctors (80%), working in geriatrics (45%) or internal medicine (14%). Ninety-two per cent of the responders assessed patients for delirium daily. The most commonly used assessment tools were the Confusion Assessment Method (52%) and the Delirium Observation Screening Scale (30%). The first-line choice in the management of hyperactive delirium was a combination of non-pharmacological and pharmacological approaches (61%). Conversely, non-pharmacological management was the first-line choice in hypoactive delirium (67%). Delirium awareness (34%), knowledge (33%), and lack of education (13%) were the most commonly reported barriers to improving the detection of delirium. Interestingly, 63% of the responders referred patients after an episode of delirium to a follow-up clinic.

**Conclusions:** This is the first systematic survey involving an international group of specialists in delirium. Several areas of lack of consensus were found. These results emphasise the importance of further research to improve care of this major unmet medical need.

**Key words:** delirium, European Delirium Association, delirium knowledge, survey, clinical practice

## Introduction

Delirium is an acute neuropsychiatric disorder characterized by inattention, other cognitive impairments, and disturbances in consciousness.

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It has a prevalence ranging from 9% to 80% depending on the setting (Inouye *et al.*, 1999; Ely, 2001; Ouimet *et al.*, 2007; Ryan *et al.*, 2013). Delirium is independently associated with increased length of stay, increased hospital costs, higher mortality, and it is a risk factor for permanent cognitive impairment (Fong *et al.*, 2009; Girard *et al.*, 2010; National Institute for Health and Clinical Excellence (NICE), 2010; Witlox *et al.*, 2010; Davis *et al.*, 2012) It is often highly distressing for patients and carers (Partridge *et al.*, 2013). Several studies have demonstrated that delirium is partially preventable (National Institute for Health and Clinical Excellence, 2010).

Despite its high prevalence and seriousness, delirium is substantially under-detected (Collins *et al.*, 2010), there are no licensed pharmacological treatments, and few national guidelines exist (National Institute for Health and Clinical Excellence, 2010). The European Delirium Association (EDA; www.europeandeliriumassociation.com) was established in 2006 with the main aims of promoting knowledge of delirium, improving clinical management, and providing support for research within Europe. The American Delirium Society (ADS; www.americandeliriumsociety.org) was recently created with similar goals, underlining the importance of coordinating clinical and research efforts to reduce the impact of delirium on short- and long-term health outcomes.

Several surveys have been conducted to evaluate the knowledge of healthcare providers with respect to delirium (Ely *et al.*, 2004; Fang *et al.*, 2008; Van Eijk *et al.*, 2008; Cadogan *et al.*, 2009; Davis and MacLullich, 2009; Patel *et al.*, 2009; Ceraso *et al.*, 2010; Forsgren and Eriksson, 2010; Mac Sweeney *et al.*, 2010; Devlin *et al.*, 2011). Four of these were conducted within Europe, one in the United States, two in South America, and one across different countries. In addition, a European survey (Leentjens *et al.*, 2008) was carried out to investigate the existence and contents of different delirium guidelines across national psychiatric associations. However, no survey has specifically targeted an international group of specialists involved in delirium care and clinical practice, and uncertainties still exist on the optimal management of delirium.

Since previous surveys were conducted, guidelines on delirium practice (National Institute for Health and Clinical Excellence, 2010) have been published by a national body within a European country (UK NICE). We were interested in surveying European clinicians with special interest in delirium to assess possible variation in practice. Our main areas of interest were assessment and diagnosis, treatment of hyperactive and hypoactive delirium, and organizational management.

## Methods

### Survey development and design

The questionnaire was constructed through an iterative process, which included item generation, construction, pilot testing, and refinement from expert members on the EDA Board. The final survey consisted of 53 questions organized into four different sections: assessment and diagnosis of delirium, treatment of hyperactive delirium, treatment of hypoactive delirium, and organizational management of delirium care (Appendix A for the full questionnaire) (see Appendixes A and B, available as supplementary material attached to the electronic version of this paper at www.journals.cambridge.org/jid_IPG).

### Survey administration

The survey period was 24 March 2012 to 11 July 2012. The invitation to participate in the online survey was distributed among the EDA membership, with additional publication on the EDA website. Reminders were sent out at one and two months after the initial survey distribution. Responses were anonymized.

### Statistical analysis

Variables were summarized using median and interquartile range (IQR) for continuous variables or proportions for categorical variables. For the purpose of the analysis, we defined experts in delirium management as those responders who (1) scored $\geq$8/10 in the self-report question: "How would you rate your knowledge of delirium"; and (2) gave a response of "more than sufficient" to the question: "How much training you have received on delirium management." The $\chi^2$ test was used to compare responses to questions on delirium assessment, and management of hyperactive and hypoactive delirium in delirium experts compared to the other responders.

## Results

### Characteristics of the responders

A total of 200 responses were collected. The majority of responders were doctors (67%), followed by nurses (14%). Respondents were mainly from European countries (United Kingdom 28.6%, Netherlands 25.3%, Italy 15%, Switzerland 9.7%, Germany 7.1%, Spain 3.8%, Portugal 2.5%, Ireland 2.5%, Sweden 0.6%, Denmark 0.6%, Austria 0.6%, United States 1.3%, Canada 0.6%, and Australia 0.6%). Most doctors worked in geriatric medicine (45%) and internal/acute

**Table 1.** Characteristics of responders

| VARIABLE[a] | N = 200 |
|---|---|
| Main occupation | |
| Doctor | 135 (67%) |
| Nurse | 29 (14%) |
| Others | 36 (18%) |
| Duration of practice | |
| Over 20 years | 20 (25%) |
| 10–19 years | 50 (34%) |
| 5–9 years | 45 (30%) |
| 1–4 years | 11 (7%) |
| <1 year | 3 (2%) |
| Training received on delirium management | |
| None | 5 (3%) |
| Very little | 17 (11%) |
| Some but sufficient | 17 (11%) |
| Sufficient | 80 (50%) |
| More than sufficient | 39 (25%) |
| Where you have received your formal training in delirium management? | |
| Medical school | 15 (10%) |
| Nursing school | 13 (2%) |
| Postgraduate education | 90 (58%) |
| Professional conferences | 47 (30%) |
| Where is your setting of practice? | |
| General hospital | 11 (6.7%) |
| General hospital affiliated to university | 76 (46%) |
| University hospital | 40 (24%) |
| General practice/community | 10 (6%) |
| Others | 28 (17%) |
| Specific setting of practice | |
| Geriatrics | 97 (45%) |
| Internal medicine/acute medicine | 30 (14%) |
| Internal medicine specialties | 9 (4%) |
| Intensive care unit | 17 (9%) |
| Emergency medicine | 4 (2%) |
| Nursing home | 4 (2%) |
| Old age psychiatry | 24 (11%) |
| Palliative care | 8 (4%) |

Notes: [a]The different total numbers in this table are due to the inability to gather a 100% response rate on each question.

medicine (14%), followed by old age psychiatry (11%), intensive care units (9%), and internal medicine specialties (4%; Table 1). Seventy per cent of the responders worked in a university hospital or general hospital affiliated to a university. Only 11.9% had received training on delirium management during their undergraduate medical or nursing school training. However, 75% rated their knowledge of delirium management as sufficient or more than sufficient.

### Assessment and diagnosis of delirium

Ninety-two per cent of responders reported that they assessed patients for delirium in their daily clinical practice. Several scales were used to assess delirium, including the Confusion Assessment Method (CAM) (52%), the Delirium Observation Screening Scale (DOSS) (30%), the CAM for the Intensive Care Unit (CAM-ICU) (13%), the Delirium Rating Scale-Revised 98 (DRS-R-98) (10%), 4 A's Test (4AT) (2%), the Cognitive Test for Delirium (0.5%), and others (4%) (Table 2). The final diagnosis was most frequently made (63.2%) using the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV), and the rest using the International Classification of Diseases-10. Once a diagnosis was made, 43.4% of the responders repeated the assessment at least once a day, with 19% twice a day, and 18.5% up to three times a day. Most of the time, the diagnosis of delirium was included in the information discharge records (91.3%).

**Table 2.** Assessment and diagnosis of delirium

| VARIABLE[a] | |
|---|---|
| Do you assess for delirium in your daily practice? | |
| Yes | 184 (92%) |
| No | 16 (8%) |
| How often you use a scale to assess for delirium? | |
| Always | 21 (26%) |
| Most of the time | 51 (26%) |
| About half of the time | 24 (12%) |
| Infrequently | 44 (22%) |
| Never | 29 (15%) |
| What tools do you use to assess for delirium?[b] | |
| Confusion Assessment Method | 104 (52%) |
| Delirium Observation Screening Scale | 60 (30%) |
| Confusion Assessment Method-ICU | 26 (13%) |
| Delirium Rating Scale-Revised 98 | 20 (10%) |
| 4AT | 4 (2%) |
| Cognitive Test for Delirium | 1 (0.5%) |
| Other[c] | 7 (4%) |
| If patients are diagnosed with delirium, how often would you review their status? | |
| Once a day | 82 (43%) |
| Twice a day | 36 (19%) |
| Three times a day | 35 (19%) |
| More than three times a day | 9 (5%) |
| Other | 27 (14%) |

Notes: [a]The different total numbers in this table are due to the inability to gather a 100% response rate on each question.
[b]Each respondent could use more than one scale.
[c]Other (tools): Mini Mental State Examination, counting backwards, Delirium-O-Meter, Memorial Delirium Assessment Scale, Richmond Agitation and Sedation Scale.

### Management of hyperactive delirium

A combination of non-pharmacological and pharmacological strategies was the dominant approach to the management of hyperactive delirium (60.6%, N = 103), while 30% (N = 51) used only a non-pharmacological protocol and 9.4% (N = 16) adopted a purely pharmacological management. A drug for the treatment of agitation in hyperactive delirium was used by 60% of the responders. Haloperidol was the most widely used antipsychotic (62%, N = 92), followed by risperidone (12%, N = 18), clozapine (5%, N = 7), and others (21%, N = 148) (Appendix B1). The most common starting dose for haloperidol was 0.5 mg (49%), with a frequency of twice a day (42%), and mainly through an oral route (76.9%) (Appendix B2). The common starting dose for risperidone was 0.5 mg (39%, N = 7). Only 61% routinely evaluated the QTc interval on the electrocardiography (ECG) before an antipsychotic was prescribed (Appendix B4). Most of the responders continued (27%, N = 32) the pharmacological treatment until delirium resolution, although we found a wide variation in the duration of treatment ranging from 1–2 days (6%, N = 7) to >8 days (6%, N = 7) (Appendix B5). A variety of interventions were included in the non-pharmacological management of hyperactive delirium (Figure 1); the most common were the evaluation of common causes of delirium (81.9%, N = 163), pain evaluation and treatment (80.4%, N = 160), assessment of constipation and urinary retention (78%, N = 156), and sensory aids (72.3%, N = 144).

### Management of hypoactive delirium

A non-pharmacological approach was the most commonly reported way of managing hypoactive delirium (67.5%, N = 108), followed by a combination of pharmacological and non-pharmacological (29.4%, N = 47) and pure pharmacological (3%; N = 5) strategies. As with the management of hyperactive delirium, in the non-pharmacological protocol, a wide variety of interventions were employed: evaluation of common causes of delirium (76.5%, N = 153), pain evaluation and treatment (71.5%, N = 143), assessment of constipation and urinary retention (71%, N = 142), and sensory aids (70%, N = 140) being the most prominent interventions (Figure 1). In the instances where a drug was prescribed (N = 67), the first choice was haloperidol (46%, N = 31), followed by risperidone (16%, N = 11), rivastigmine (7%, N = 5), and others (31%, N = 30) (Appendix B).

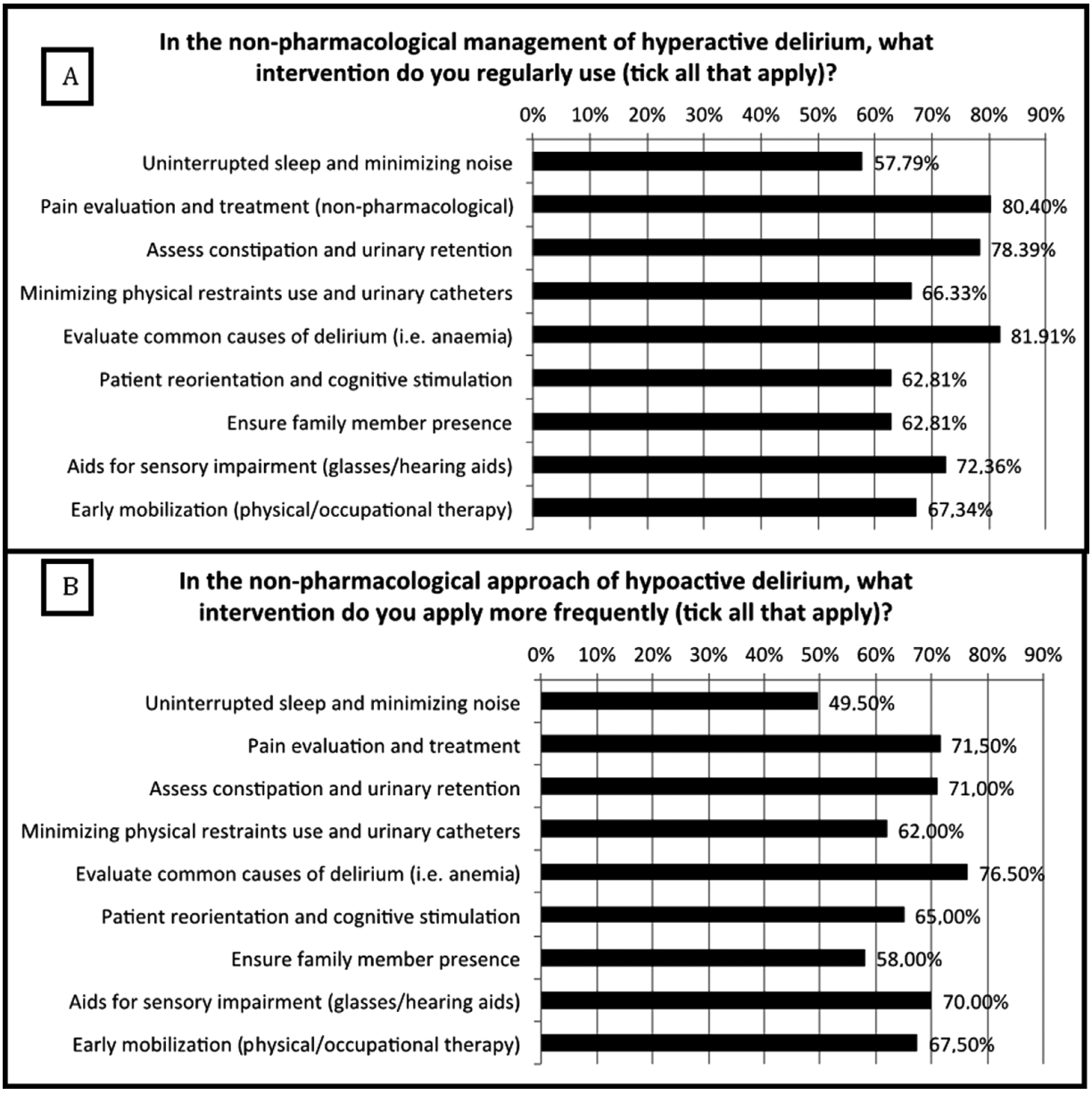


**Figure 1.** Interventions for the management of hyperactive (panel A) and hypoactive (panel B) delirium.

## Delirium work-up

In terms of investigations, doctors frequently ordered laboratory analyses (58.5%), and neuroimaging studies such as brain CT (26.5%) and MRI (26.5%). Less frequently, electroencephalogram (9.5%) and lumbar punctures (6%) were performed to investigate the causes of delirium.

## Organizational management

A minority of the responders either agreed (41.7%) or strongly agreed (4%) that delirium was well managed in the clinical setting where they worked. Eighty per cent of the participants believed that delirium is under-detected in their setting. However, the majority (78%) reported that their institutions had specific guidelines for delirium.

Delirium awareness (34%), knowledge/incompetence (33%), lack of education (13.2%), and lack of time for assessment (8.8%) were identified as the four main barriers to improving delirium detection (Appendix B6). Similarly, poor knowledge (24.4%), staffing issues (24.4%), poor education (13.3%), and poor attitudes (4.5%) were the main barriers to improving delirium management (Appendix B7).

After discharge, follow-up was performed by 63% of the responders. Specifically, 15.3% assessed only those patients being discharged to home, 18.5% referred patients to a memory clinic if either the cognitive impairment did not resolve

or there was a pre-existing cognitive impairment (10.6%), and 11.9% assessed regardless of cognitive impairment at discharge. Interestingly, 6.6% of the participants reported a referral to a dedicated delirium follow-up clinic.

### Comparison of delirium management between experts and non-experts

Within the sample, there were 67 participants who could be identified as being experts in delirium care. Compared to the rest of the sample, these experts were more likely to use haloperidol as a first-line drug for the management of agitation in hyperactive delirium ($p = 0.010$) and to use a non-pharmacological intervention as the first approach for the management of hypoactive delirium ($p = 0.01$) (Appendix B8). No other significant differences were detected in the use of drugs or approach to the management of hyperactive and hypoactive delirium.

## Discussion

This is the first international survey of practice among professionals with an interest in delirium. The survey found areas of both agreement and disagreement. There was substantial consensus in many aspects of the assessment and management of hyperactive and hypoactive delirium. In particular, the majority stated that they assessed for delirium frequently and this information is included in the medical records. A large proportion of clinicians reported using a non-pharmacological approach alone or combined with a pharmacological intervention to manage hyperactive delirium. There is inconsistency on the use of antipsychotic drugs to decrease symptoms of agitation in hyperactive delirium, although haloperidol was the most frequently used drug for this purpose. Interestingly, about half of the clinicians start with a low dose, using an oral route in almost 80% of the patients. Similarly, the management of hypoactive delirium is mainly approached with non-pharmacological strategies and rarely by pharmacological treatments. However, only 61% of the responders routinely used ECG in the context of antipsychotic prescription, despite this being recommended by guidelines. Finally, delirium experts reported a significantly higher proportion of haloperidol use as a first-line treatment of hyperactive delirium and a non-pharmacological approach as the first intervention for the management of hypoactive delirium.

In 2010, NICE published the first national guidelines on delirium diagnosis, prevention, and management (National Institute for Health and Clinical Excellence, 2010). These guidelines recommended that the short version of the CAM and the CAM-ICU (for critical care patients) could be used as alternatives to DSM-IV to diagnose delirium. This is in accordance with our findings, given that 52% used the CAM and 13% used the CAM-ICU. Interestingly we also found that 30% of the responders used the DOSS for delirium screening. All the responders in our survey performed the final diagnosis according to standard diagnostic criteria, using either the DSM-IV (63.2%) or the ICD-10 (36.8%).

The NICE guidelines (National Institute for Health and Clinical Excellence, 2010) provided recommendations on non-pharmacological and pharmacological interventions for delirium treatment, without differentiating between the hyperactive and hypoactive form. The guidelines suggested that first there should be a non-pharmacological approach, identifying and managing underlying causes, providing reorientation, and involving family and carers. In this survey, respondents were more aligned with these guidelines in the case of hypoactive delirium, with a 67.5% prevalence of an exclusively non-pharmacological intervention and a 29% prevalence of a mixed approach, i.e. pharmacological and non-pharmacological. With hyperactive delirium, there was a higher prevalence of the mixed approach (60.6%) and a lower prevalence of the pure non-pharmacological management (30%). These findings suggest that drugs are commonly used in the *initial* management of both hypoactive and hyperactive delirium. This indicates substantial divergence from the evidence-based recommendations in the NICE guidelines, since the NICE guidelines only support the use of haloperidol or olanzapine to control patients who are considered at risk for themselves or others and when a non-pharmacological approach (i.e. verbal and non-verbal techniques) have failed.

In our survey, haloperidol was the first-line drug used to treat hyperactive delirium despite its unproven efficacy and the absence of official bodies' approval for this indication and as recently reported by Meagher and colleagues (2013). The findings of haloperidol being the most frequently prescribed drug are in line with previous surveys in ICU and non-ICU settings (Ely *et al.*, 2004; Fang *et al.*, 2008; Van Eijk *et al.*, 2008; Cadogan *et al.*, 2009; Davis and MacLullich, 2009; Patel *et al.*, 2009; Ceraso *et al.*, 2010; Forsgren and Eriksson, 2010; Mac Sweeney *et al.*, 2010; Devlin *et al.*, 2011). The type of antipsychotics reported in our survey also confirms the data reported by Meagher (2010) on delirium experts attending a workshop of the EDA, organized to explore the attitude toward delirium pharmacotherapy. In fact,

about 66% of the participants to the workshop indicated haloperidol as their first choice to treat delirium. The information on the suggested daily dose (0.5–15 mg/day) cannot directly be compared to our data because we gathered information on the starting dose. The higher doses reported by Meagher (2010) might also have been related to a higher prevalence of ICU healthcare providers in the workshop audience.

Interestingly, about 32% of the responders continued pharmacological treatment until delirium resolution. The use of antipsychotics until delirium resolution might reflect the indications of the NICE guidelines, which support a treatment for one week or less. Nonetheless, about 12% of the responders use a pharmacological treatment "as long as required." This approach could be supported by the persistence of delirium in about 17% of elderly patients discharged from hospital after acute hospitalization (Cole *et al.*, 2009). Nonetheless, antipsychotics are used for the treatment of symptoms of agitation in delirium and there is no clear indication for their use in the hypoactive delirium. The continuation of treatment might indeed expose hospitalized patients to a higher risk of cardiovascular events and mortality, especially in older patients having pre-existing dementia (Maher *et al.*, 2011).

The NICE guidelines (National Institute for Health and Clinical Excellence, 2010) reported information only on extrapyramidal signs as side effects of antipsychotics, but there is no mention on the cardiac effects and the need for ECG monitoring. We did not investigate in our survey the use of specific scales to measure extrapyramidal side effects, but we did gather information on the ECG monitoring. There have been cases of QTc prolongation and torsades de pointes (TdP) after high doses of intravenous (IV) administration of haloperidol, and it has been suggested that patients receiving low doses ($<2$ mg per day) of haloperidol with no risk factors for prolonged QTc or TdP, and with a normal QTc on a baseline ECG should not receive continuous ECG monitoring (Meyer-Massetti *et al.*, 2010). If cumulative doses are $>2$ mg per day, patients should be placed on telemetry (Meyer-Massetti *et al.*, 2010). In our studied population we found that most of the responders use an oral route (76.9%), followed by IV administration when haloperidol is used. Interestingly, 34% perform an ECG evaluation or a single rhythm strip before starting the drug and 6.3% performed continuous heart monitoring. The latter may reflect the presence of ICU physicians in the responders' group.

Another key point is the difference in strategies for investigation of delirium. Currently, there are no specific indications on the type and sequence of tests for the evaluation of patients with delirium. We found that doctors frequently order laboratory analyses to rule out the causes of delirium, which reflect a reasonable approach since an infection or electrolyte unbalances are frequent triggers. However, little is known on the risk and benefit of ordering instrumental tests (i.e. neuroimaging, electroencephalogram (EEG), or lumbar punctures) (Morandi *et al.*, 2010). Unnecessary tests might be detrimental for the patients, possibly leading to an increased severity of delirium and exposing the patients to a greater risk of complications. If delirium affects one in five patients (Inouye *et al.*, 1999; Ely, 2001; Ouimet *et al.*, 2007; Ryan *et al.*, 2013), deciding who with delirium should receive an instrumental evaluation is extremely important also for the rational use of healthcare resources.

Interestingly, neither the NICE guidelines nor previous surveys have mentioned follow-up after an episode of delirium, although it has been reported an association between delirium, cognitive impairment, and worsening dementia. (Fong *et al.*, 2009; Girard *et al.*, 2010; Davis *et al.*, 2012). In our cohort of responders, we found different approaches but most importantly 60% of responders follow up patients after an episode of delirium, and even more interestingly, in almost 7% of the cases there are dedicated delirium follow-up clinics. The importance of referring patients with cognitive impairment/dementia to a memory clinic has been shown previously (Morgan *et al.*, 2009). Early detection of dementia is critical to ensuring that persons having dementia and their caregivers have access to treatment, education, counseling, and other services that can delay decline, prevent crises, ease caregiver burden, and delay institutionalization. At the same time, the establishment of follow-up clinics also provides the opportunity to identify potentially treatable causes in patients for whom delirium resolves before hospital discharge and for those with persistent delirium.

Another important domain of the survey was the assessment of the perceived barriers to improve the education and management of delirium. Improvement of education and management of delirium is limited, as we found by both individual level barriers and organizational/cultural barriers. This concept has been introduced by Teodorczuk and colleagues (2012) after conducting two workshops within two EDA meetings in 2010 and 2011 to specifically identify what are the main barriers to improve the detection of delirium and to provide a "call for action" plan at individual, organizational, and societal levels to improve recognition.

The principal way in which this survey differs from previous work is in the choice of respondent population, a group of specialist delirium practitioners. Other surveys on delirium diagnosis and management have mainly been of healthcare providers working in an ICU (Ely *et al.*, 2004; Van Eijk *et al.*, 2008; Cadogan *et al.*, 2009; Patel *et al.*, 2009; Ceraso *et al.*, 2010; Forsgren and Eriksson, 2010; Mac Sweeney *et al.*, 2010), focusing on tools to assess for delirium, sedation practice, and the pharmacological management of delirium. Haloperidol was reported as the most commonly used drug to treat delirium, and the CAM-ICU was the most frequently used tool to assess for delirium, followed by the Intensive Care Delirium Screening Checklist. Two other surveys have targeted ICU pharmacists and junior doctors (Davis and MacLullich, 2009; Devlin *et al.*, 2011). The survey of pharmacists (Devlin *et al.*, 2011) specifically reported on the pharmacological treatment of delirium, and practice with regard to the safety of treatment with ECG monitoring. The survey of junior UK doctors (Devlin *et al.*, 2011) identified gaps in confidence in diagnostic and management skills with respect to delirium. In each of these surveys, consistent with our findings, haloperidol was reported as the first-line treatment of delirium.

To our knowledge this is the first online survey to explore attitudes of delirium recognition and management in a healthcare providers with a special interest in delirium. Nonetheless, several limitations should be mentioned. We were able to obtain a high level of responses mainly from just six European countries (United Kingdom, Netherlands, Italy, Spain, and Switzerland). The lower rate of responses from other countries might reflect our inability to reach providers with an interest in delirium or it may simply reflect an increased level of interest in delirium in these particular countries. The second important limitation was the inability to gather a 100% response rate on each question. The third limitation relates to the possible contrast between self-report practice and actual practice, and this could be the base for future quality improvement projects. Finally, we have not addressed which are the main interventions for the prevention of delirium. This information should be included in future investigations.

In conclusion, this is the first survey involving an international group of professionals with a special interest in delirium care. Across different responses, we found areas of both common practice and lack of consensus (i.e. initial drug use, delirium work-up evaluation, post-delirium follow-up), underlying the gaps between clinical guidelines recommendations and clinical practice. These issues highlight areas of future research, including syntheses of existing evidence, the opportunity to monitor temporal trends and to detect future changes of practice, and to provide key elements to support further education on the emerging topic of delirium.

## Conflict of interest

Authors report no financial conflicts of interest. Funding/support: Daniel Davis receives funding as a Wellcome Trust Research Training Fellow. A Morandi and D Davis are the members of The University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology, part of the cross-council Lifelong Health and Wellbeing Initiative. Funding from BBSRC, EPSRC, ESRC, and MRC is gratefully acknowledged. Dr Olofsson is supported by the Strategic Research Programme in Care Sciences, Sweden.

## Description of authors' role

Study conception and design was done by all the authors. Acquisition of data was done by A. Morandi and D. Davis. Data analysis was done by J. K. Taylor. Interpretation of results was done by all the authors. Manuscript was drafted by A. Morandi. Critical revision of the manuscript was done by all the authors. Final approval of the manuscript was done by all the authors.

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